UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/827,854	04/05/2001	Vassilis L Zannis	07180/004003	6635

21559 7590 01/25/2005

CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
NGUYEN, QUANG	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 01/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/827,854	ZANNIS ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-47,50,51,53-62,64-72,74 and 76-78* is/are pending in the application.

4a) Of the above claim(s) *32,35,38-42 and 45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30,31,33,34,36,37,43,44,46,47,50,51,53-62,64-72,74 and 76-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment filed on 10/26/04 has been entered.

This application contains claims 32, 35, 38-42 and 45 drawn to non-elected species without traverse in Applicants' response dated 1/9/03. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Amended claims 30-31, 33-34, 36-37, 43-44, 46-47, 50-51, 53-62, 64-72, 74 and 76-78 are examined on the merits herein, with SEQ ID NO:15 (apoE3) and adenoviral vector as the elected species.

Claim Objections

Amended claims 50-51 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. This is because the polypeptide region in claim 30 from which both claims 50-51 are dependent has at least 90% sequence identity to the corresponding region of amino acid residues 1-185 of SEQ ID NO:2 (apoE3, not any human apoE polypeptide). Claims 50-51 are therefore broader than the claims from which they depend.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

With respect to the elected invention and species, amended claims 30-31, 33-34, 36-37, 43-44, 46-47, 50-51, 53-62, 64-72, 74 and 76-78 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method of lowering cholesterol in a mammal that lacks an endogenous normally functioning apoE gene, said method comprises administering intravascularly into said mammal a recombinant replication defective adenovirus containing a nucleic acid encoding a polypeptide selected from a group consisting of: the amino acid residues 1-185 of SEQ ID NO:2, the amino acid residues 1-202 of SEQ ID NO:2, the amino acid residues of 1-229 of SEQ ID NO:2 and the amino acid residues of 1-259 of SEQ ID NO:2, wherein said polypeptide is expressed and the total serum cholesterol level in said mammal is lowered without inducing hypertriglyceridemia,

does not reasonably provide enablement for a method of lowering cholesterol in any mammal without inducing hypertriglyceridemia by intravascular administering to said mammal any vector comprising a nucleic acid molecule, including a recombinant adenovirus containing a nucleic acid encoding a polypeptide having fewer than 299 amino acids, wherein said polypeptide comprises a region of at least 150 amino acids having at least 90% sequence identity to the corresponding region of amino acid residues 1-185 of SEQ ID NO:2. The specification does not enable any person skilled

in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for the same reasons already set forth in the previous office action mailed on 4/21/04 (pages 6-17).

Response to Arguments

Applicant's arguments related to the above rejection in the Amendment filed on 10/26/04 (pages 9-18) have been fully considered, but they are not found persuasive.

1. With respect to claim breadth, Applicants argue simply that the amended claims are within the scope of enablement provided by the specification, notably that amended claim 30 now requires the nucleic acid encoding the truncated apoE protein to be contained within a vector, the encoded polypeptides are now to be 90% identical to amino acids 1-185 of SEQ ID NO:2 and that the route of administration is limited to intravascular administration.

Please note that the scope of amended claim 30 and its dependent claims is still not the same as the enabled scope given in the previous office action mailed on 4/21/04 (pages 6-17). Apart from the specific route of administration, the claims still encompass a method of lowering cholesterol in any mammal (e.g., a mammal lacking an endogenous normally functioning apoE gene, a mammal lacking an endogenous normally functioning LDL receptor or a mammal having any lipid disorder) without inducing hypertriglyceridemia using any vector (e.g., viral or non-viral vectors, including carriers such as cells administered by bone marrow transplantation) as long as it comprises a nucleic acid encoding a polypeptide having fewer than 299 amino acids,

and the polypeptide comprises a region of at least 150 amino acids having at least 90% sequence identity to the corresponding region of amino acid residues 1-185 of SEQ ID NO:2.

2. With respect to the general unpredictability of the art, Applicants simply asserts that it is Applicants' work that removes the unpredictability in the use of vectors encoding apoE polypeptide fragments for lowering plasma cholesterol without increasing hypertriglyceridemia. Applicants further argue that the Dang reference relates specifically to the future of cancer gene therapeutics, and the Romano reference does not demonstrate that gene therapy does not work, but rather it demonstrates that some optimization is necessary and this only requires routine experimentation. Additionally, Applicants argue that Kawashiri's conclusion that viable gene therapy approaches for lipid disorders are inadequate was made in 2000 and Kawashiri did not have the benefit of reviewing Applicant's method that was not published in the scientific literature until 2001. Furthermore, human testing is not required, for enablement purposes, to support claims of an *in vivo* utility. With respect to the results of Kashyap and Tsukamoto, Applicants argue that their work demonstrates that their gene methods are similar to that of the present invention, but using a full length apoE protein, are capable of imparting a therapeutic effect by lowering plasma cholesterol in a relevant animal model. With respect to the Yoshida reference, Applicants argue that the Yoshida method differs from the method of the present application in two critical ways namely, the use of a full length apoE protein rather than a fragment and performing a

bone marrow transplantation rather than the intravascular administration of an expression vector as required by the instant claims. With respect to the Kypreos reference, Applicants argue that the present invention encompasses apoE fragments having a C-terminal truncation sufficient to ablate the hypertriglyceridemic effect of the full protein, and therefore there is no need to identify the specific amino acids responsible for the effect because, to fall within the claims, those amino acids are necessarily deleted.

Contrary to Applicants' assertion and mischaracterization of the cited references that the attainment of any therapeutic effect, for this instance lowering total serum cholesterol level without inducing hypertriglyceridemia in any mammal, via gene therapy is routine and predictable, the examiner notes that if the attainment of any therapeutic effect via gene therapy is routine and predictable as asserted by Applicants, then why does Romano still state "Despite the latest progress reported in the area of vector design, research strategies still have to tackle critically important issues, such as further improvement of gene transfer technology, especially for *in vivo* gene delivery applications, regulation and control of the transgene expression post-cell transduction, and a variety of complex safety matters. These three main issues are to some extent intertwined and pose severe limitations on the applications of gene transfer technology in therapy" (page 21, col. 1, first paragraph). In October 2000, Kawashiri et al. also state "Somatic gene therapy is a viable approach to the therapy of several lipid disorders for which therapies are currently inadequate" and "The **next decade is therefore likely to witness** several clinical trials of gene therapy for lipid disorders"

(see Conclusion section, page 125). Even in 2001, Applicants in the publication of Kypreos et al. (FASEB J. 15:1598-1600, 2001) still state "One major parameter in successful gene therapy approaches is gene dosage and expression levels....The inability of the truncated apoE forms that lack all or part of the carboxyl-terminal 260-299 region to induce hypertriglyceridemia, coupled with their intact ability to clear cholesterol, makes them **attractive candidates in future gene therapy applications to correct remnant removal disorders**" (page 1600, col. 2, last paragraph). Although human data are not required, the scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art.

The unpredictability of the biological activity of the ApoE proteins to maintain cholesterol and triglyceride homeostasis *in vivo*, specifically in ApoE-deficient mice, is also supported at least by the results of Tsukamoto et al., Kashyap et al., Yoshida et al., let alone for any mammal in need thereof. Contrary to the results obtained by the present invention using full-length human ApoE, both Tsukamoto et al. and Kashyap et al. indicated that under their experimental conditions the infection of ApoE-deficient mice with a recombinant adenovirus capable of expressing a mature, full-length human ApoE (299 amino acids) resulted in a reduction in the plasma total cholesterol level without induction of hypertriglyceridemia. In addition, Yoshida et al. showed that ApoE-deficient mice receiving apoE-/- bone marrow cells that express human apoE3 or apoE2 or apoEcys142 have cholesterol levels increasing with age and the cholesterol levels are not affected by apoE expression (see abstract). Please also note that as written in the claims, a vector also encompasses a cell expressing a recombinant human apoE

because it comprises an exogenous nucleic acid encoding a human apoE. Moreover, Athanasopoulos et al. also demonstrated that intramuscular plasmid injection in apoE-/- mice with plasmid vectors expressing allelic human apoE2 or apoE3 isoforms **did not result in any reduction of plasma cholesterol nor in plasma triglycerides** compared to control injected mice (see Table 1, and abstract). Thus, it is abundantly clear that the biological activity of the ApoE proteins to maintain cholesterol and triglyceride homeostasis in ApoE-deficient mice is highly variable depending on the experimental conditions used, let alone for any mammal in need of treatment using a vector as broadly claimed by the present invention.

With respect to the Kypreos reference and Applicants' argument that the present invention encompasses apoE fragments having a C-terminal truncation sufficient to ablate the hypertriglyceridemic effect of the full protein, and therefore there is no need to identify the specific amino acids responsible for the effect, please note that as written the claims **do not encompass only apoE fragments having a C-terminal truncation**. The encoded polypeptide may still possess the carboxyl-terminal region of any mature, native human apoE as long as the polypeptide has fewer than 299 amino acids and it comprises a region of at least 150 amino acids having at least 90% sequence identity to the corresponding region of amino acid residues 1-185 of SEQ ID NO:2.

3. With respect to the amount of direction or guidance presented, Applicants argue that none of the references cited by the examiner demonstrates that the instant specification fails to enable the invention as presently claimed. With respect to the

Kawashiri reference, Applicants argue basically that there is no teaching in the reference that disparages the use of apoE-/- mice as a model **for other lipid disorders**. Additionally, with respect to the Orkin reference Applicants argue that Orkin does not find that all animal models are unsatisfactory and that Orkin does not even consider an animal model of hypercholesterolemia. With respect to the teachings of Dijk and Linton, Applicants argue that that their results which show that over-expression of apoE in a lipoprotein receptor-deficient (LDLR-/-) mouse does not correct the hypercholesterolemia are expected because it is well known that the LDLR is a downsteam apoE receptor. Furthermore, the fact that apoE over-expression fails to correct hypercholesterolemia in an LDLR-/- is irrelevant to the question of whether the apoE-/- model used by Applicants enables the claimed invention because Applicants' model is not LDLR-deficient. With respect to the teachings of Yoshida, Applicants point out that the method of Yoshida is completely unrelated to Applicants' method which intravascularly injects a vector expressing a homologous apoE protein fragment. Additionally, the basic finding of Yoshida that expression of an exogenous apoE increases, rather than decreases, plasma cholesterol is contrary to the vast majority of the scientific evidence, see for example the teachings of Dijk and Linton. Thus, Applicants argue that it is most likely that the lack of therapeutic effect reported by Yoshida et al. was merely a defect in experimental design which once optimized would yield the opposite result.

With respect to the cited Kawashiri reference, there is no indication in either the Kawashiri or in the prior art that the apoE-/- mouse model **is an acceptable model for**

any lipid disorder. Particularly, the biological activity of the ApoE proteins to maintain cholesterol and triglyceride homeostasis in ApoE-deficient mice is highly variable depending on the experimental conditions used as already discussed in the preceding paragraphs, let alone for any mammal having any lipid disorder. Although the Orkin reference does not discuss specifically any animal model of hypercholesterolemia, the main point is that mouse models often do not faithfully mimic the relevant human conditions and that animal models are not satisfactory for studying many important disorders. Applicants do not provide any objective evidence indicating that ApoE-deficient mouse model is an acceptable model for any lipid disorder and that this mouse model mimics all the relevant conditions for all human lipid disorders (Please note that claims 74 and 76-78 are directed specifically to a gene therapy method for treating human).

With respect to the teachings of Dijk and Linton, please note that the term "mammal" in the instant claims encompasses a mammal that lacks an endogenous, normally functioning low density lipoprotein receptor (see dependent claim 46, for example). Both Dijk and Linton clearly demonstrated that over-expression of apoE in a lipoprotein receptor-deficient (LDLR-/-) mouse does not correct the hypercholesterolemia. Applicants failed to provide any guidance for a skilled artisan on how to lower the total serum cholesterol level without inducing hypertriglyceridemia in LDLR-/- mice, let alone for any LDLR-/- mammal as broadly claimed, and which is contradictory to the results reported by Dijk and Linton.

With respect to the Yoshida reference, as already discussed above please note that a vector also encompasses a cell expressing a recombinant human apoE because it comprises an exogenous nucleic acid encoding a human apoE and as written the claims do not encompass only apoE fragments having a C-terminal truncation. Thus, the breadth of the claims encompasses the method of Yoshida which reported negative results. The results obtained by Yoshida coupled with variable results reported by other groups as already discussed above highlighted the unpredictability of the biological activity of the ApoE proteins to maintain cholesterol and triglyceride homeostasis in ApoE-deficient mice, let alone for any mammal in need of treatment.

4. Examiner further notes that Applicants fail to adequately address the issue of "a nucleic acid encoding a polypeptide having fewer than 299 amino acids as long as it comprises a region of at least 150 amino acids having at least 80% sequence identify to any mature, native, human apoE polypeptide" as set forth in the previous office action on pages 14-15. The same reasons set forth in the previous office action are also applied to the instant amended claims. For example, the instant specification fails to provide sufficient guidance for a skilled artisan on which modification(s), for example deletion, insertion or substitution, in which combination(s), and at which amino acid residues in any mature, native, human apoE polypeptide, including apoE3 as the elected species, so that the modified polypeptide still possesses the desired properties (lowering the total serum cholesterol level without inducing hypertriglyceridemia in a mammal). As is well recognized in the art, any modification (even a "conservative"

substitution) to a critical structural region of a protein is likely to significantly alter its functional properties. Particularly, the encoded polypeptide in the broad claim as written may still possess the carboxyl-terminal region of a mature, native, human apoE as long as the polypeptide comprises a region of at least 150 amino acids having at least 90% sequence identity to the corresponding region of amino acid residues 1-185 of SEQ ID NO:2. Then it is unclear which modification(s) can be carried out to the rest of the polypeptide, so that the polypeptide still possesses the desired properties despite the retention of a carboxyl-terminal region of a mature, native, human apoE polypeptide that is known to contribute to hypertriglyceridemia *in vivo*? Furthermore, there is no evidence of record or in the prior art at the effective filing date of the present application that any truncated apoE polypeptide, including truncated apoE3, that is 184 amino acid residues in length or less is still capable of lowering total serum cholesterol level *in vivo*.

To further support the examiner's position on the above unpredictable claimed embodiment, Guo et al. (PNAS 101:9205-9210, 2004) estimated that only about a third of single amino acid changes would completely inactivate the average protein and increasing the number of substitutions additively increases the probability that the protein would be inactivated and that specific proteins may be more or less tolerant to changes (see the entire article).

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Irem Yucel, Ph.D., at (571) 272-0781.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service

center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

Quang Nguyen, Ph.D.

DAVID GUZO
PRIMARY EXAMINER